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October 16, 2013

VIA REGULATIONS.GOV

Office of Environmental Information (OEI) Docket (Mail code 2822T)

Attn: **Docket ID Numbers EPA-HQ-ORD-2009-0229 and EPA-HQ-ORD-2013-0111**

Re: Draft Literature Search Strategies, Preliminary Evidence Tables, and Preliminary Exposure-Response Arrays for Ethyl *tert*-Butyl Ether and *tert*-Butyl Alcohol for the Integrated Risk Information System (IRIS) Toxicological Reviews of Ethyl *tert*-Butyl Ether (ETBE) and tert-Butanol

The American Petroleum Institute (API) is the primary trade association for the oil and gas industry in the United States and its membership includes more than 400 companies engaged in all aspects of the oil and gas industry, including the exploration, production, refining, transportation and marketing of crude petroleum and petroleum products. API is pleased to submit comments on submit comments on Docket ID No. EPA-HQ-ORD-2009-0229 and EPA-HQ-ORD-2013-0111

1. Introduction

The American Petroleum Institute (API) is the primary trade association for the oil and gas industry in the United States and its membership includes more than 400 companies engaged in all aspects of the oil and gas industry, including the exploration, production, refining, transportation and marketing of crude petroleum and petroleum products. API is pleased to provide these comments to EPA in response to the Agency's request for comments on Preliminary Materials for the Integrated Risk Information System (IRIS) Toxicological Review of Ethyl *tert*-Butyl Ether (ETBE) and *tert*-Butyl Alcohol (*tert*-Butanol), dated July 2013.

We applaud efforts by EPA to improve the IRIS assessment process and we support implementation of the enhancements unveiled in the Agency's July 31, 2013 announcement[1]. We agree that increased stakeholder engagement and identification of scientific issues early in the process should result in marked improvement in both the quality and timeliness of IRIS assessments.

In their Federal Register notice (78 FR 48674), EPA requested comments on draft literature search strategies, preliminary evidence tables, and preliminary exposure-response arrays,

[1] http://www.epa.gov/IRIS/process.htm

including comments on clarity and transparency of the materials, the approach for identifying pertinent literature, the selection of studies for data extraction, methodological considerations affecting interpretation or confidence in study results, and identification of additional relevant studies. A summary of our major comments addressing these and other aspects of the materials released for ETBE and *tert*-Butanol are provided below, followed by more detailed discussion.

Summary of Major Comments

- The scope of the assessments to be conducted, and the problem(s) to be addressed are not described in the materials released by EPA. Defining these elements are important prerequisites to gathering relevant data.
- EPA should consider the current status of these substances as fuel additives in defining the scope and formulating problems to be addressed.
- Some aspects of the literature search strategy for these substances should be improved, notably: inclusion of studies conducted under the requirements of the Clean Air Act, Section 211(b); review of ECHA's database of information submitted in support of REACH registration of these substances; consideration of the relationship of *tert*-Butanol data to evaluation of ETBE systemic toxicity; and consideration of excluded exposure studies and environmental fate studies in defining scope and problem formulation.
- Indication of critical studies, the rationale for selection, and data quality must be included in Evidence Tables in order to meet the Agency's stated goals for the enhanced IRIS process. This information is needed to frame scientific issues, identify uncertainties and direct research.
- Mode of Action (MOA) data should be considered in selecting pertinent data for Evidence Tables (e.g. male rat kidney effects).
- The Maltoni et al., 1999 study of (ETBE) should be evaluated in light of the National Toxicology Program's (NTP) subsequent review, and any assessment of data from this study should reflect the findings of NTP's review.
- Tumor promotion data for ETBE should be removed from the Evidence Tables and Exposure Response-Arrays, since well conducted chronic rodent bioassays have been reported for this substance.

2. What Scope/Problem is being Addressed?

EPA did not provide an opportunity for a public scoping/problem formulation meeting for these substances as described in the IRIS process enhancements announcement. The implication is therefore that these considerations have been completed without public input. However, the preliminary materials released by the Agency do not speak to this stage of the review process, nor do they identify the scope and the problem that presumably have been already defined and are to be addressed by the assessments. As the enhanced IRIS process clearly indicates, these elements are important prerequisites to gathering data and evaluating

their relevance. EPA should identify the scope, define the problem and provide supporting information. We ask that the Agency consider the following factors in defining the scope and problem to be addressed:

A. ETBE as a Fuel/Fuel Additive in the US

Numerous states have banned the use of ETBE and other aliphatic ethers as oxygenates in gasoline. While ETBE does remain registered with EPA for use as a gasoline additive, it is not currently being used for this purpose anywhere in the US. However, it is used as a gasoline additive in Japan and in Europe.

B. *Tert*-Butanol as a Fuel/Fuel Additive in the US

Tert-Butanol is no longer registered as a fuel or fuel additive in the US; therefore, it cannot be used in gasoline unless EPA re-approves such use.

3. Literature Search

The EPA preliminary materials provide clarity and transparency regarding the literature search strategy, and the linkage to the HERO database for details is useful. We offer the following specific comments regarding improvements that could be made to the literature search strategies for these substances.

A. Improving the approach for identifying pertinent literature

EPA has done a generally good job of identifying existing literature on ETBE and *tert*-Butanol health effects. Incorporation of the ETBE studies conducted by the Japan Petroleum Energy Center, which were identified under the "Additional Search Strategies" is a particular case in point. There are, however, several aspects of the literature search strategies for these substances which we believe should be improved:

i. Clean Air Act Section 211(b) Studies

A number of studies sponsored by the API under the requirements of Section 211(b) of the Clean Air Act were not cited. These were studies carried out on a "light ends" mixture of gasoline and fuel additives, including ETBE or *tert*-Butanol. Although the ETBE immunotoxicity study from this test program was cited by EPA (White, K.L., 2002[2]), other studies of subchronic toxicity, neurotoxicity, genotoxicity, developmental toxicity, and reproductive toxicity were not cited. These missing studies should be included in the List of References for completeness sake, even if they are not considered to be key studies. A listing of the studies conducted and the existing docket/document ID numbers are provided in Attachment 1.

ii. EPA's process should include review of the ECHA database

[2] White, KL. (2002) Immunological evaluation of gasoline ETBE vapor condensate in female Sprague-Dawley rats using the plaque forming cell assay. ImmunoTox, Inc. under contract to Huntingdon Life Sciences, Richmond, VA; Project No. ITI 901. Unpublished report.

Full registrations for ETBE and *tert*-Butanol have been filed under the EU REACH regulations and the supporting dataset is available on the ECHA website. This information can be found for ETBE at:
http://apps.echa.europa.eu/registered/data/dossiers/DISS-9ebd98b4-66aa-4922-e044-00144f67d031/DISS-9ebd98b4-66aa-4922-e044-00144f67d031_DISS-9ebd98b4-66aa-4922-e044-00144f67d031.html.
and can be found for *tert*-Butanol at:
http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d805cf7-5096-6923-e044-00144f67d249/DISS-9d805cf7-5096-6923-e044-00144f67d249_DISS-9d805cf7-5096-6923-e044-00144f67d249.html
As required by REACH regulations, characterization of the ETBE and *tert*-Butanol datasets includes systematic evaluation of the data quality for each study according to criteria defined by Klimisch et al., 1997[3]. Any testing proposals to address weaknesses or gaps in the existing datasets as required by REACH are also identified in the registration and included in the ECHA database. It is recommended that EPA routinely review and include information from the ECHA database as part of their process for gathering preliminary materials for IRIS risk assessments. The ECHA datasets for ETBE and *tert*-Butanol should be incorporated into EPA's preliminary materials before proceeding with preparation of the draft assessment.

iii. Relationship of ETBE and *tert*-Butyl Alcohol (*tert*-Butanol) data
Tert-Butanol has been shown to be the primary metabolite of ETBE in mammals. EPA should consider whether the *tert*-Butanol information is useful to the evaluation of ETBE systemic toxicity and its Mode of Action (MOA).

iv. Exposure Studies (ETBE)
EPA excluded three human exposure studies and 72 biodegradation and environmental fate studies identified in the ETBE literature search as not pertinent to the risk assessment. EPA should explain whether these studies were considered in defining the scope of the assessment and in problem formulation.

4. Screening Strategy and Preliminary Evidence Tables

The organization of information in the form of evidence tables is a useful construct to aid presentation. However, the preliminary materials provided by EPA fail to meet expectations based on the Agency's characterization of the enhanced IRIS process. In the subject announcement (78 FR 48676) the Agency states:

"Releasing the draft literature search strategy, preliminary evidence tables, and exposure response arrays early will ensure that critical research is not omitted and communicates to the public why critical studies were chosen for further evaluation,

[3] Klimisch HJ, Andreae M and Tillman U. (1997) A systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. *Regl Toxicol Pharm* 25: 1-5.

helping frame major scientific issues and ultimately leading to more efficient production of assessments."

The preliminary materials do not indicate which studies the Agency believes are the critical ones and the rationale for selection of these studies. Uncertainties and issues associated with the existing health effects database, and the key scientific issues anticipated to be addressed in the course of developing the assessment are likewise not addressed in the preliminary materials. Providing context around these aspects of the information is needed for a constructive discussion of the available data. It is also vital for assessing the relevance of ongoing research and, even more important, new research that could be initiated to address study deficiencies and enhance the overall quality of the assessments. Instead of providing their views, the Agency states:

"No studies were excluded based on study quality considerations, so as to allow for public input on methodological considerations that could affect the interpretation of or confidence in each study's results."

The problem with this approach is that there is no way to discern which studies EPA considers (even from a preliminary perspective) to be important. If the public meeting to comment on these preliminary materials is going to be both the first and last public opportunity for discussion prior to release of the draft assessment, EPA staff should make available their preliminary views on these matters and the rationale should be clear and transparent. Without this information, it will not be possible to have a constructive discussion of the critical studies, their uncertainties, and the possible opportunities to address limitations. We strongly recommend that the Agency include this information in the preliminary materials provided for public comment during this step of the new IRIS process, or alternatively schedule an additional public meeting to discuss these issues. The Agency's preliminary evaluation of the quality of individual studies using defined and accepted criteria, such as the Klimisch scoring approach referenced in comment 3.A.(ii), as well as an indication of the relevance of key data for quantitation of human risk, should also be provided.

In addition to the general comments provided above, the following specific concerns are identified.

1. **Mode of Action (MOA) data should be considered in selecting pertinent data for Evidence Tables**

   EPA does not include data on possible mechanisms of toxicity in the preliminary evidence tables. Inclusion and consideration of mode of action data is an important aspect of selecting pertinent studies for human health risk assessment. In the case of ETBE, mode of action data regarding male rat kidney effects that may not be relevant to humans is an excellent example of the need for consideration of such data early in the process. EPA's view of existing MOA data and how it will influence selection of critical

data for risk assessment is fundamental to understanding whether this is a scientific issue to be addressed and to identifying useful research to explore any issues. We ask that EPA identify any MOA considerations that influence the selection of pertinent/critical studies when they provide preliminary evidence tables for review.

2. **Maltoni et al., 1999 (ETBE)**

EPA identified in its List of References for ETBE the cancer bioassay by Maltoni et al., 1999[4]. This study has been widely criticized on technical grounds and was the subject of an extensive review by a group of pathologists from the National Toxicology Program(NTP)[5]. EPA previously announced that it would not use lymphoma and leukemia data from the Maltoni study in further considerations of the carcinogenic potential of ETBE[6,7]. While it is understandable that this study would be included in the List of References, some mention should be made of the previous concerns and EPA's conclusions regarding data quality in the Maltoni study. We also ask that EPA include documentation of NTP's review of this work in the list of references.

EPA also chose to include data from the Maltoni study in the preliminary Evidence Tables and preliminary Exposure-Response Arrays. The tumor data provided in the preliminary Evidence Tables are different from those included in the NTP Summary Report[5]. We strongly recommend that data from the original Maltoni paper be removed from both the Evidence Tables and Exposure Response Arrays. If EPA chooses to include data from this study, it should be based on the findings of the NTP pathology working group.

3. **Tumor Promotion Studies (ETBE)**

EPA chose to include the tumor promotion study of Hagiwara et al., 2011[8] in the preliminary Evidence Tables and preliminary Exposure Response Arrays for ETBE. This is another example that highlights the need for more information/clarity regarding EPA's thinking about the significance of data and whether they are pertinent to human health risk assessment. EPA's 2005 Guidelines for Carcinogen Risk Assessment comments on the use of tumor initiation-promotion data, stating:

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[4] Maltoni, C; Belpoggi, F; Soffritti, M; et al. (1999) Comprehensive long-term experimental project of carcinogenicity bioassays on gasoline oxygenated additives: plan and first report of results from study of ethyl-tertiary-butyl-ether (ETBE). Eur J Oncol 4:493−508.

[5] Malarkey DE and Bucher JR. Summary Report of the National Toxicology Program and Environmental Protection Agency-Sponsored Review of Pathology Materials from Selected Ramazzini Institute Rodent Cancer Bioassays. November 29, 2011

[6] http://www.epa.gov/iris/ramazzini.htm

[7] Gift JS, et al., (2013) Scientific Considerations for Evaluating Cancer Bioassays Conducted by the Ramazzini Institute. Environ Health Perspect. Sep 17. [Epub ahead of print]

[8] Hagiwara, A; Doi, Y; Imai, N; et al. (2011) Medium-term multi-organ carcinogenesis bioassay of ethyl tertiary-butyl ether in rats. Toxicol 289(2−3): 160−166.

> *"It is important to recognize the limitations of these experimental protocols, such as short duration, limited histology, lack of complete development of tumors, or experimental manipulation of the carcinogenic process, that may limit their contribution to the overall assessment. Generally, their results are appropriate as aids in the interpretation of other toxicological evidence (e.g., rodent chronic bioassays)"*

We recommend that these data be removed from the Evidence Tables and Exposure Response-Arrays since well conducted chronic rodent bioassays have been reported for ETBE and are included in the EPA materials.

4. **Structure of Evidence Tables and Exposure-Response Arrays for Carcinogenic Effects**

   There is an inconsistency in the approaches used by EPA to construct the Evidence Tables and Exposure-Response Arrays of carcinogenic data for ETBE and *tert*-Butanol. Separate tables for carcinogenic data are presented for ETBE, while cancer data are incorporated into the organ specific data for *tert*-Butanol. We recommend that a consistent approach be adopted for presenting data across substances.

5. Preliminary Exposure-Response Arrays

The Exposure-Response Arrays provide a helpful format for presentation of data from pertinent studies. As indicated in earlier comments, the Arrays will be more useful at this stage of the process when the Agency indicates which data are judged to be critical for assessment of human risk.

Attachment 1

Clean Air Act Section 211(b) Health Effects Studies of "Light Ends" of Gasoline Containing Oxygenates

	13-week repeat-dose study including immunotox, neurotox, and genotox satellite studies in rats	Developmental Toxicity in Rats	Developmental Toxicity in Mice	Reproductive Toxicity in Rats	Chronic/Cancer Study in Rats	Pharmacokinetics
Baseline Gasoline	EPA-HQ-OAR-2003-0065-0403	EPA-HQ-OAR-2003-0065-0503	EPA-HQ-OAR-2003-0065-0555	EPA-HQ-OAR-2003-0065-0514	EPA-HQ-OAR-2003-0065-0611	ND
Gasoline w/MTBE	EPA-HQ-OAR-2003-0065-0418	EPA-HQ-OAR-2003-0065-0539	EPA-HQ-OAR-2003-0065-0530 EPA-HQ-OAR-2003-0065-0581	EPA-HQ-OAR-2003-0065-0690	EPA-HQ-OAR-2003-0065-0608	ND
Gasoline w/ETOH	EPA-HQ-OAR-2003-0065-0558	EPA-HQ-OAR-2003-0065-0486	ND	EPA-HQ-OAR-2003-0065-0521	ND	ND
Gasoline w/TAME	EPA-HQ-OAR-2003-0065-0699	EPA-HQ-OAR-2003-0065-0490	ND	EPA-HQ-OAR-2003-0065-0526	ND	ND
Gasoline w/ETBE	EPA-HQ-OAR-2003-0065-0678	EPA-HQ-OAR-2003-0065-0493	ND	EPA-HQ-OAR-2003-0065-0687	ND	in progress
Gasoline w/DIPE	EPA-HQ-OAR-2003-0065-0728	EPA-HQ-OAR-2003-0065-0718	ND	EPA-HQ-OAR-2003-0065-0697	ND	in progress
Gasoline w/TBA	EPA-HQ-OAR-2003-0065-0733	EPA-HQ-OAR-2003-0065-0551	ND	EPA-HQ-OAR-2003-0065-0695	ND	EPA-HQ-OAR-2003-0065-0725

MTBE – methyl *tert*-butyl ether
ETBE – ethyl *tert*-butyl ether
ETOH – ethanol
DIPE – diisopropyl ether
TAME – *tert*-amyl methyl ether
TBA – *tert*-Butanol